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10/798,111	03/10/2004	Dario Norberto R. Carrara	88066-7900	5916

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EXAMINER	
SCHLIENTZ, NATHAN W	
ART UNIT	PAPER NUMBER
1616	

NOTIFICATION DATE	DELIVERY MODE
12/23/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/798,111	CARRARA ET AL.	
	Examiner	Art Unit	
	Nathan W. Schlientz	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 November 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-11,13,15-26,29-31,37,40-47 and 56-68* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-11,13,15-26,29-31,37,40-47 and 56-68* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 29 November 2010 has been entered.

Status of Claims

Claims 1, 3-11, 13, 15-26, 29-31, 37, 40-47 and 56-68 are pending and are presently examined herein on the merits for patentability. No claim is allowed at this time.

Response to Amendment

The declaration filed on 29 November 2010 under 37 CFR 1.131 has been considered but is ineffective to overcome the WO 02/22132 reference.

The declaration states that attached hereto are pages that describe an invention that was made prior to the March 11, 2002 publication date of WO 02/22132 to Gray et al. ("Gray"). All of the information shown on attached pages was completed prior to March 21,2002 and disclose various transdermal and transmucosal formulations for

administration of active agents using compositions that include a delivery vehicle, permeation enhancers and other components.

The examiner respectfully asserts that the evidence attached to the declaration is not commensurate in scope with the instant claims. The instant claims are substantially free of long-chain fatty alcohols, long-chain fatty acids and long-chain fatty esters. The instant specification states that "substantially free" means an amount which does not impart a perceptible odor to the formulation at a distance of 1 meter. Such formulations are also deemed to be substantially odor free. For the purpose of example and illustration, a formulation comprising fatty alcohols, fatty acids and/or fatty esters in an amount of less than about 0.04% by weight of the formulation is substantially odor free.

However, the evidence attached to the declaration states that it .is an object of the present invention to provide a skin permeation enhancer composition comprising of a first component that is *a saturated fatty alcohol or fatty acid* given by the formula CH_3-$(CH_2)_n$-CH_2OH or CH_3-$(CH_2)_n$-CH_2COOH respectively, in which n is an integer from 8 to 22, preferably 8 to 12, most preferably 10 or an unsaturated fatty alcohol or fatty acid given by the formula CH_3-$(C_nH_{2(n-x)})$-OH or CH_3-$(C_nH_{2(n-x)})$-COOH respectively in which n is an integer from 8 to 22. The evidence also states that the compositions in accordance with the present invention contain *a fatty alcohol, preferably lauryl alcohol or dodecanol in about 0.1 to about 20.0 %w/w on the whole composition; preferably from about 0.4 to 10.0 %w/w and more preferably 0.2 to 3.0 %w/w.*

The evidence further states that in another aspect, the present invention relates to a method for administering topically or systemically active agent(s), comprising: 1. An

active agent(s); 2. A ternary vehicle composite (composed by a C1-C4 alkanol, a glycol and water); 3. A penetration enhancers combination (*fatty alcohol or acid* and diethylene glycol monoethyl ether); 4. A gelling agent and 5. A pH regulator. It has been discovered that in a transdermal formulation comprising different group of drugs as active agents; *lauryl alcohol* and diethylene glycol monoethyl ether as penetration enhancers, in a ternary vehicle composite comprised of ethanol, propylene glycol and purified water, using a polymer or copolymer of acrylic acid, preferably a carbomer as gelling forming, provides therapeutically effective serum concentration of each active agent throughout at least a 24 hours period.

Therefore, the evidence clearly teaches that fatty alcohols or fatty acids are included the invention at a concentration that is above the instantly claimed allowable amount. The instant claims do not allow for more than 0.04% by weight of fatty alcohol, fatty acid or fatty ester, whereas the evidence teaches compositions comprising 0.1-20% by weight fatty alcohol or fatty acid.

Withdrawn Rejections

Rejections and/or objections not reiterated from the previous Office Action are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set of rejections and/or objections presently being applied to the instant application.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

1. Claims 1, 3-8, 10, 11, 13, 15, 20, 22, 37, 40-43, 45-47, 56, 57, 60-62 and 68 are rejected under 35 U.S.C. 102(a) as being anticipated by Gray et al. (WO 02/22132; US 7,030,104 is the English-language equivalent and is relied upon herein).

Gray et al. disclose in Table 1 gel formulations (Reference G29-287, G29-299 and Tx11323) for percutaneous administration wherein the gels comprise:

REFERENCE	G29-287	G29-299	Tx11323 batch-12
NAc (nomegestrol acetate)	0.4	0.4	—
Estradiol	—	0.1	0.1
Carbopol 1342 or 1382	0.5	0.5	0.5
Propyleneglycol	6	6	6
Transcutol	5	5	5
Solketal			
EDTA	0.05	0.05	0.05
Triethanolamine	0.3	0.3	0.3
Demineralized water	42.75	42.65	43.05
95° Ethanol	45	45	45

Gray et al. also disclose topically administering two gel formulations A and B (Table 5), depicted below, to women by spreading 3 g of gel per day over 400 cm^2 (col. 13, ln. 1-25).

TABLE 5

formula of the 2 gels used for pharmacokinetic trials in women

	Gel A	Gel B
Nomegestrol acetate	0.40	0.40
Propylene glycol	8.00	8.00
Solketal	3.00	3.00
Carbopol 980	0.60	
Carbopol 1382		0.50
EDTA	0.05	0.05
TEA	0.24	0.30
95° Ethanol	45.00	45.00
Demineralized water	42.69	42.73

Gray et al. further disclose that topically administering gel TX11323 (shown above) at a rate of 3 g of gel on a body area of 400 cm^2 leads to plasmatic levels of estradiol at the equilibrium of approximately 40 pg/ml, which are located in the area of effective plasmatic concentrations of estradiol as these are comprised between 30 and 60 ng/ml (col. 14, ln. 1-6). Gray et al. disclose that estradiol gels likely to produce satisfactory clinical results must present during in vitro tests of percutaneous passage cumulative quantities of estradiol at 24 hours of greater than 1.05 µg without exceeding 2.1 µg so as not to induce hyperestrogenosis (col. 14, ln. 7-15).

Therefore, Gray et al. disclose a gel comprising:

- a hormone (nomegestrol acetate, a progestin, at 0.4 wt.% (G29-287); estradiol, an estrogen, at 0.1 wt.% (Tx11323 batch-12); or a combination thereof (G29-299));
- a gelling agent (Carbopol 1342 or 1382) at 0.5 wt.%;
- an alkanol (95° ethanol) at 45 wt.%;
- a polyalcohol (propylene glycol) at 6 wt.%;
- a permeation enhancer (Transcutol® (diethylene glycol monoethyl ether), or Solketal) at 5 wt.%;
- a neutralizing agent (triethanolamine) at 0.3 wt.%;
- a sequestering agent (EDTA) at 0.05 wt.%; and
- water at 42.65-43.05 wt.%.

Gray et al. disclose administering the gels to women for to determine the pharmacokinetic behavior or percutaneous administration for hormonal treatment of perimenopause and menopause as well as ovarian hormonal deficiencies (col. 1, ln. 15-19; col. 2, ln. 12-16; and col. 14, ln. 1-15).

Response to Arguments

Applicant does not specifically argue the instant rejection, but rather relies on the declaration under 37 CFR 1.131 to overcome the rejection. However, as discussed above, the declaration is not commensurate in scope with the instant claims and thus is not sufficient to overcome the instant rejection.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in Graham v. John Deere Co., 383 U.S. 1,148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

2. Claims 1, 3-11, 13, 15-26, 29-31, 37, 40-47 and 56-68 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gray et al. (WO 02/22132; US 7,030,104; and US 2003/0181430), in view of Dudley et al. (US 6,503,894), Labrie (US 5,955,455), Catherino et al. (J. Steroid Biochem. Molec. Biol., 1995) and Wang et al. (The Journal of Clinical Endocrinology and Metabolism, 2000).

Determination of the scope and content of the prior art

(MPEP 2141.01)

The teachings of Gray et al. are discussed above and incorporated herein by reference.

Ascertainment of the difference between the prior art and the claims

(MPEP 2141.02)

With regard to instant claims 23-25, Gray et al. do not specifically recite that the free serum concentration of estradiol is increased to about 8.8 ng/dl, nor increases in serum levels of estrone to about 10.4 ng/dl or 193 ng/dl. However, Gray et al. teach that topically administering gel TX11323 (estradiol gel) at a rate of 3 g of gel on a body area of 400 cm^2 leads to plasmatic levels of estradiol at the equilibrium of approximately 40 pg/ml, which are located in the area of effective plasmatic concentrations of estradiol as these are comprised between 30 and 60 ng/ml (col. 14, ln. 1-6). Gray et al. teach that estradiol gels likely to produce satisfactory clinical results must present during in vitro tests of percutaneous passage cumulative quantities of estradiol at 24 hours of greater than 1.05 µg without exceeding 2.1 µg so as not to induce hyperestrogenosis (col. 14, ln. 7-15). Therefore, it would have been well within the purview of one of

ordinary skill in the art to administer enough estradiol gel according to Gray et al. in order to achieve desired free serum concentrations of estradiol as well as serum level increases of estrone.

With regard to instant claims 9, 16-19, 21, 26, 27, 29, 30, 44 and 64-67, Gray et al. do not teach their topical hormonal compositions to comprise an androgen or a progestin as listed in claim 21. However, Dudley et al. teach topical formulations for treating hypogonadism in males comprising androgenic steroids or progestogens (col. 11, ln. 63 to col. 12, ln. 1; and Table 5). Dudley et al. teach that the composition comprises an androgenic steroid, such as testosterone, methyltestosterone and/or methandrostenolone (col. 11, ln. 63 to col. 12, ln. 1), or a progestogen, such as anagestone, chlormadinone acetate, delmadinone acetate, etc. (col. 12, ln. 2-13); a C1-C4 alcohol, such as ethanol (col. 12, ln. 17-18); a penetration enhancer, such as diethylene glycol monoethyl ether (col. 12, ln. 54-55); a thickener, such as Carbopol (col. 12, ln. 60-67); and water (col. 12, ln. 17-22). Dudley teaches a testosterone gel named AndroGel® that comprises 1 wt.% testosterone (Table 5). Therefore, it would have been well within the purview of one of ordinary skill in the art to use the appropriate hormones, such as testosterone at 1 wt.%, methyltestosterone and methandrostenolone, or a progestogen, in the formulations of Gray et al. for treating a person for hypogonadism. Also, Catherino et al. teach that megestrol acetate and nomegestrol acetate differ only at the 19 position, and that nomegestrol is a clinically useful progestin and an effective contraceptive agent when used as an implant (pg. 239, right column, ln. 3-7; and pg. 243, left column, last line to right column, ln. 7). Thus, it

would have been obvious for one of ordinary skill to substitute megestrol acetate in the place of nomegestrol acetate, as they differ only in the absence of a methyl at the 19 position and are both useful progestins.

With regard to instant claims 31 and 59, Labrie teaches that dehydroepiandrosterone (DHEA) is useful for the treatment of hypogonadism and conditions related to decreased secretion of sex steroid precursors by the adrenals (Abstract). Therefore, it would have been *prima facie* obvious for one of ordinary skill in the art to use DHEA in the formulations of Gray et al. in order to treat hypogonadism.

With regard to instant claims 58 and 63, Gray et al. do not teach a kit comprising a container that retains their compositions and includes a pump for dispensing a predetermined dosage or volume of the formulation upon demand. However, delivering hormone gels via actuation of a pump is readily known in the art, as shown by Wang et al. wherein hydroalcoholic gels containing 1 wt.% testosterone were packaged in multidose bottles with an actuator pump for treatment of hypogonadal males (pg. 2840, right column, "T gel and patch").

Finding of prima facie obviousness

Rational and Motivation (MPEP 2142-43)

Therefore, it would have been *prima facie* obvious for one of ordinary skill in the art at the time of the invention to treat hypogonadism with the compositions of Gray et al., using as the androgen testosterone, methyltestosterone, methandrostenolone, DHEA or combinations thereof, and as the penetration enhancer diethylene glycol monoethyl ether, as reasonably taught by Dudley et al. and Labrie et al. Further, it

would have been *prima facie* obvious for one of ordinary skill in the art at the time of the invention to package the hydroalcoholic gels into multidose bottles with an actuator pump for dispensing predetermined dosages, as reasonably taught by Wang et al.

With regard to the combination of methyltestosterone and methandrostenolone, such would have been obvious in the absence of evidence to the contrary because it is generally prima facie obvious to use in combination two or more ingredients that have previously been used separately for the same purpose to form a third composition useful for that same purpose. The idea of combining them flows logically from their having been taught individually in the prior art. *In re Kerkhoven* 626 F.2d 646, 850, 205 USPQ 1069, 1072 (CCPA 1980).

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Response to Arguments

Applicant does not specifically argue the instant rejection, but rather relies on the declaration under 37 CFR 1.131 to overcome the rejection. However, as discussed above, the declaration is not commensurate in scope with the instant claims and thus is not sufficient to overcome the instant rejection.

Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nathan W. Schlientz whose telephone number is (571)272-9924. The examiner can normally be reached on 9:00 AM to 5:30 PM, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann R. Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

NWS

/John Pak/
Primary Examiner, Art Unit 1616